Annual Reporting Form for SCEDDBO Projects and Cores

Center Overview

Period covered by the report: 5/1/2010 – 4/30/2011
EPA Agreement Number: RD83329301-0
Investigators: Marie Lynn Miranda, Allison Ashley Koch, Richard Auten, W. Michael Foster, Alan Gelfand, Pamela Maxson, Evan Myers, Jerome Reiter, Geeta Swamy, Redford Williams
Project Period: Year 4

Objectives of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO)

The central mission of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes is to determine how environmental, social, and host factors jointly contribute to health disparities. Specific aims of the Center are:

1. *To develop and operate an interdisciplinary children's health research center with a focus on understanding how biological, physiological, environmental, and social aspects of vulnerability contribute to health disparities;*
2. *To enhance research in children's health at Duke by promoting research interactions among programs in biomedicine, pediatric and obstetric care, environmental health, and the social sciences and establishing an infrastructure to support and extend interdisciplinary research;*
3. *To develop new methodologies for incorporating innovative statistical analysis into children's environmental health research and policy practice, with a particular emphasis on spatial, genetic and proteomic analysis;*
4. *To serve as a technical and educational resource to the local community, region, the nation, and to international agencies in the area of children's health and health disparities*; *and,*
5. *To translate the results of the Center into direct interventions in clinical care and practice*.

SCEDDBO leverages and promotes active partnerships among the Nicholas School of the Environment, the Duke University Medical Center, Trinity College of Arts and Sciences, and Duke's Children's Environmental Health Initiative, as well as the Durham County Health Department (DCHD), and the Lincoln Community Health Center (LCHC). The Center brings together the expertise of obstetricians, pediatricians, genetic epidemiologists, spatial statisticians, environmental scientists, social epidemiologists, social psychologists, geographers, and community organizations. SCEDDBO capitalizes on substantial ongoing commitments by Duke University to foster strong interdisciplinary research programs in environmental health sciences.

Synthesis across SCEDDBO. **Research Project A: Mapping Disparities in Birth Outcomes** provides population-level research on health disparities in birth outcomes. Spatially-linking 1.7 million birth records with environmental, social, and host factor data layers allows for population-level analysis of potential co-factors identified in both the clinical obstetrics **Research Project B: Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in**

Birth Outcomes and mouse model **Research Project C: Perinatal Environmental Exposure Disparity and Neonatal Respiratory Health** studies. The data from Research Project A is spatially linked in GIS to the data from Research Project B.

The neighborhood assessment undertaken in Research Project B provides important neighborhood-level environmental and social data to Research Project A. In addition, the environmental data developed for Research Project A works synergistically with the mouse model work in Research Project C. For example, the air quality data from Research Project A is being used to further refine experimental dose design in Research Project C. In turn, results from Research Project C regarding experimental effects of multiple environmental agents on fetal growth restriction and postnatal somatic and lung development help point to locations in North Carolina where we are looking more closely at air quality impacts on birth outcomes in Research Project A.

Thus Research Project A is an epidemiological study, while Research Project B is a complementary clinical obstetrics project. Both projects focus on how combined environmental, social, and host factors shape disparities in birth outcomes. Research Project B also allows for additional host factor analysis. Research Project C uses a mouse model system to explore how disparities in exposure and response to exposure initiate and/or enhance disparities in birth outcomes and subsequent neonatal respiratory health. Like Research Projects A and B, Project C explores the effects of *combined* environmental exposures to prototypical air pollutants common in North Carolina (particulate matter and ozone), as well as social stress, on fetal growth restriction, neonatal somatic growth, and subsequent lung development and function.

The synergy among the research projects is facilitated by the GIS and Statistical Analysis (GISSA) Core. The GISSA Core allows for data analysis of the very large amount of data through the use of high-end GIS applications in combination with Bayesian spatial hierarchical modeling and other advanced spatial statistical approaches, thus permitting multi-level analysis. Research Projects A and B both apply a Bayesian spatial hierarchical modeling approach to capture uncertainties in pregnancy outcomes and to elucidate the contributions of economic, sociocultural, and environmental stressors on health disparities in pregnancy outcomes. State-of-the-art GIS methods allow for sophisticated spatial statistical analyses at highly resolved spatial scales.

The GISSA Core also provides the analysis of the biological response and genetic data generated in Research Projects B and C. The rich source of social, environmental, and host data in Project B, coupled with sophisticated statistical genetic approaches for identifying gene-gene and gene-environment interactions, provides the opportunity to make important discoveries of how these higher order interactions may be working together to promote or prevent adverse birth outcomes. By serving as a central clearinghouse for statistical analysis, the GISSA Core tracks outcomes in each project and uses these discoveries to guide the analysis in each of the other projects.

The Community and Outreach Translation Core (COTC) facilitates the communication of findings from our large-scale study and future more-focused investigations. The COTC supported the implementation of the neighborhood assessment undertaken in Research Project B and has helped to communicate the results of the assessment to community partners. In addition, the COTC draws on the GISSA Core to develop materials that communicate the results of the research projects in formats and applications that are immediately accessible to the lay public.

SCEDDBO is characterized by significant synergies among center components. To provide concrete examples of how the work of the center is moving forward in a collaborative way, here we highlight four areas: air pollution, social context of environmental stress, the Community Assessment Project, and statistical methods development. We provide summaries in this center overview; additional details can be found in the individual center component write-ups.

Air Pollution. To investigate the relationship of air pollution exposure and pregnancy outcomes, we have examined air pollution in all three projects. In Projects A and B, we have used criteria air pollutant data from the EPA AQS monitoring network, as well as CMAQ and FUSED modeling data. In addition, we have recently obtained highly resolved air toxics data. These data have been spatially linked to the births in both Projects A and B. In addition, we have created a road proximity measure which can be used in both Projects A and B. The road proximity measures allow us to consider a relatively simple metric for assessing risk of exposure to air pollution, specifically traffic-related air pollution which includes particulate matter and diesel exhaust, both of which are being investigated within Project C. We have already published several manuscripts on the relationship between air pollution and pregnancy outcomes and anticipate several more in Year 5. We are also preparing a manuscript that synthesizes the air pollution work done across projects to be submitted during year 5.

The Social Context of Environmental Stress. We continue to work toward synthesis across all three projects. We have been able to combine our knowledge of the pregnant women in Project A with our rich data from the pregnant women in Project B. With our access to the North Carolina Detailed Birth Record (DBR) in Project A, we have been able to link participants in Project B with their birth certificate data. Using maternal and infant identifying information, including name, place, and date of birth, we have been able to link 1349 (99.0%) participants who completed the study and had a live birth by December 31, 2009 and 96 (79.3%) participants that were lost-to-follow-up but with an expected delivery date on or before December 31, 2009. This linkage will allow us to examine multiple questions including racial residential segregation, residential mobility, and maternal medical complications.

Additionally, the effects of resource deprivation suggested by findings in Projects A and B prompted Project C to add a resource deprivation (nesting restriction) component in order to test the proof-of-principle that the combination of multiple stressors/environmental contaminants may affect health even when the individual exposures do not.

Community Assessment Project/Built Environment. An important measure of potential environmental stress is the built environment. Our Community Assessment Project assessed built environment variables for over 17,000 tax parcels, including the home addresses of over 40% of the participants in the Healthy Pregnancy, Healthy Baby Study (SCEDDBO Project B). Analyses of the built environment data are underway. Seven scales (housing damage, property disorder, security measures, tenure, vacancy, violent crime and nuisances) have been constructed at five levels of geography (census block, primary adjacency communities, census block group, census tract, and city-defined neighborhoods). The continuous and categorical scale variables have been merged with the Durham birth records (Project A) and with the clinical OB participants' records (Project B), which enables multiple analyses of the relationships among the built environment, psychosocial health, and pregnancy outcomes. The second wave of data collection is planned for year 5.

Statistical Methods Development. We are pursuing three projects that capitalize on combining information in the data for Project A and Project B. The first project is to utilize the fine detail in Project B data to improve analyses involving Project A data.

The second project is to use the Project B data to check the sensitivity of conclusions from Project A analyses to potential unmeasured confounding. This is accomplished by comparing the findings from models fit using Project A data with the findings from parallel models fit using Project B data that control for additional relevant variables available only in Project B. If the associations found in the Project A models remain robust after including the potential confounders from Project B, our confidence in the conclusions increases. We are working on methods that perform such tests in a principled, model-based manner. In a related project, we also are checking the sensitivity of conclusions from Project A analyses to possible measurement errors in the data. For example, educational attainment variables for mothers in the intersection of Project A and Project B are quite different on the two datafiles. We treat Project B education values as truth—since we are more confident in their accuracy—and replace the Project A education values with this new truth. For mothers in the intersection of the datasets, we then can re-run analyses to see if results change dramatically. We also are working on imputing corrected values of education for the entire Project A data.

The third project is to explore factors that affect maternal blood pressure during pregnancy. This project involves combining pollution data from Project A with other data from Project B. We consider a variety of statistical approaches for this project, including latent trajectory and sparse functional data models. In the latter approach, we introduce a low-dimensional set of latent factors to predict blood pressure curves. Environmental, social, and genetic factors are used to help explain variation in the blood pressure trajectories. Our ultimate goal is to link these predicted trajectories to birth outcomes; for example, women with monotonically-increasing blood pressure trajectories may exhibit poorer birth outcomes than women with U-shaped curves. Methodological extensions include joint modeling of blood pressure and air pollution trajectories via structural equation models.

Publications

Miranda, ML, Edwards, SE.. Use of Spatial Analysis to Support Environmental Health Research and Practice. 2011 *North Carolina Medical Journal*. 72(2):132-135.

Administrative Core

Period covered by the report: 5/1/2010– 4/30/2011
EPA Agreement Number: RD83329301-0
Investigators: Marie Lynn Miranda, Richard Auten, Pamela Maxson
Project Period: Year 4

Objectives of Core

The Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO) is governed through an Administrative Core that includes an Executive Committee composed of the Director, a Co-Director, and the Project Manager; an Internal Steering Committee composed of members of the Executive Committee and the Directors of the Research Projects and the Facility and Community Outreach Cores; and an External Advisory Committee composed of senior environmental health scientists, as well as community representatives, with expertise relevant to SCEDDBO, who provide informal consultation, as well as annual formal evaluation of Center research and outreach activities.

The specific aims of the Administrative Core are to:

a. Provide scientific direction and leadership;
b. Coordinate and foster interactions among research project and facility core investigators;
c. Provide administrative services for the Center;
d. Direct the Young Investigators program; and
e. Represent Duke's SCEDDBO to the university, the community, the NIH, other Children's Environmental Health Centers across the United States, and the policy and scientific community interested in children's environmental health more broadly.

In all activities, SCEDDBO emphasizes the importance of diversity. The decision to focus on health disparities, the gender and racial diversity of Center leadership, the incorporation of natural, social, and biomedical scientists, a commitment to community-based participatory research, and efforts to promote the careers of promising new investigators are all indicative of the importance that we place on fostering environments where all people can prosper.

Progress Report/Summary of Accomplishments

Quality Management Plan. The Administrative Core continued to distribute the Quality Management Plan (QMP) to all new SCEDDBO collaborators. These individuals are required to sign the cover sheet thereby agreeing to abide by the policies laid out in the QMP. The Administrative Core keeps a copy of these signed forms in its files. In addition, the Administrative Core continued the internal audit on the participant data files for Project B: Healthy Pregnancy, Healthy Baby Study for quality assurance purposes. This is expected to be completed during year 5.

Young Investigators Program. Richard Auten and Marie Lynn Miranda continue to mentor Geeta Swamy. Marie Lynn Miranda continues to serve as Dr. Stapleton's mentor.

Year Four Expenditures. Year four expenditures matched projections in most areas. Spending on lab costs, particularly environmental and genetic analysis, was higher than anticipated, largely due to increased external costs such as increased participant capture. Spending was slightly lower than budgeted for personnel costs due to personnel shifts that occurred throughout year four.

IRB Certification. A centralized database on IRB and IACUC certification and continuing education requirements is maintained through the Administrative Core. Twice a year, Dr. Pamela Maxson, the QA Manager, verifies that all researchers associated with SCEDDBO have completed their basic certification and continuing education requirements (one credit of continuing education is required each year to maintain certification). Reminders are sent to investigators when they are due for additional training. In addition, Dr. Maxson is responsible for ensuring IRB and IACUC Protocols are renewed and updated as necessary. All of these documents are posted to the SCEDDBO internal website, and paper copies are centrally maintained by Dr. Maxson.

Meetings. The Executive Committee typically met monthly, in advance of the Internal Steering Committee meetings, in order to set the agenda for the larger monthly all-hands meetings. We held a retreat in May of Year 4 to plan for the upcoming year, as well as to discuss how best to position SCEDDBO for renewal.

Website. The Administrative Core provided material on SCEDDBO to the EPA for uploading to the EPA children's centers website. In addition, we updated our SCEDDBO website, linked off the website for the Children's Environmental Health Initiative (www.nicholas.duke.edu/cehi).

We continue to use our secure internal website that allows for discussion boards, email communication, and document storage associated with the work of each of the SCEDDBO components.

Dissemination. Numerous talks were given throughout the year by SCEDDBO investigators at a variety of different conferences as described in the research project write-ups below. In addition, Dr. Miranda was the keynote speaker at our Nurses Conference, Environmental Considerations in Nursing Practice in May, 2010. She also spoke at the Environmental Health Summit in September, 2010. SCEDDBO also co-sponsored a symposium "The Social Context of Environmental Exposures in Children" in March, 2011. Speakers from Harvard, the United States Environmental Protection Agency, the National Institute of Child Health and Human Development, and Duke University discussed the role of the social context of environmental exposures in children. The symposium was well attended and garnered much positive feedback.

Training opportunities. We provided multiple training opportunities to SCEDDBO investigators and research staff. These opportunities included both intensive short course and semester long coursework for several research staff, as well as travel to professional meetings for researchers supported on the SCEDDBO grant. We also offered training workshops through our Community Outreach and Translation Core, with administrative support provided through the Administrative Core.

New Collaborations. As part of our mission to both support the work of young investigators and advance the research mission of SCEDDBO, we continue our collaborations with Dr. Staci Bilbo, Assistant Professor, Department of Psychology and Neuroscience, Duke University and Dr. Rebecca Fry, Assistant Professor, Gillings Global School of Public Health, UNC. We continue working with Dr. Bilbo on mouse models to explore the joint impact of environmental and social stressors on birth and developmental outcomes. We are working with Dr. Fry to explore gene expression and epigenetic changes associated with *in utero* metals exposures, with a particular emphasis on cadmium. We have submitted grant applications to NIH and the EPA. In addition, we continue our CDC-funded collaboration with Dr. Heather Stapleton, Assistant Professor, Nicholas School of the Environment, Duke University. This study leverages our ongoing clinical obstetrics project to assess *in utero* exposures to brominated flame retardants, as well as the relationship between brominated flame retardant body burden and maternal thyroid function. To maximize power and resources, we extended our data collection for this collaboration into year 5. We have also written grant applications to the NIH to support further development of this work.

Personnel. Martha Keating, the COTC director, relocated to the US EPA in October, 2010. In addition, Dr. Evan Myers joined our Project A team in Year 4. Lastly, Dr. Sherman James resigned from his position on the executive team in preparation for his upcoming retirement.

National Service. Duke agreed to host the Children's Environmental Health Centers' monthly conference calls, and she helped organize the October 2010 Children's Centers conference. In addition, Dr. Miranda now serves as a standing member of the Children's Health Protection Advisory Committee. Dr. Miranda also serves as a chartered member of the NIH's Infectious Diseases, Reproductive Health, Asthma and Pulmonary Conditions (IRAP) Study Section. Multiple SCEDDBO investigators help to review proposals for federal funding agencies, as well as review manuscripts for peer-reviewed journals.

Research Project A: Mapping Disparities in Birth Outcomes

Period covered by the report: 5/1/2010 – 4/30/2011
EPA Agreement Number: RD83329301-0
Investigators: Marie Lynn Miranda (PI), Alan Gelfand, Pamela Maxson, Evan Myers
Project Period: Year 4

Objectives of Research

The central objective of Project A is to determine whether and to what extent joint exposures to socioeconomic and environmental stressors contribute to racial and ethnic health disparities in poor pregnancy outcomes. Using a geographically-based nested study design moving from analysis of births for the entire State of North Carolina to six demographically and geographically distinct counties to a single health center and state-of-the-art Geographic Information Systems applications with Bayesian spatial hierarchical modeling and other advanced spatial statistical approaches, the specific aims are to:

1. Spatially link detailed birth record, fetal death certificates, socioeconomic, environmental, tax assessor, community-based, and clinical obstetric data at highly resolved scales for the State of North Carolina from 1990-2003;
2. Refine the concept of fetal growth restriction by a) developing a joint distribution for birthweight and gestation using bivariate modeling for live births and fetal deaths – both separately and jointly, and b) defining it in terms of fetal and infant mortality, rather than percentile cut points; and
3. Determine whether and to what extent differential exposures to both environmental and social stressors help explain health disparities in fetal growth restriction among a) African-American women compared to Non-Hispanic white and Hispanic women, b) Older African-American women compared to younger African-American women, c) Hispanic women compared to Non-Hispanic white and African-American women, and d) Foreign born Hispanic women compared to US born Hispanic women.

This project evaluates a large number of factors in diverse populations, providing broad relevance for birth outcomes across time, space, and demography. Identifying social and environmental factors contributing to fetal growth restriction will improve our understanding of disease etiology and explain the racial disparity in disease incidence, leading to effective interventions against poor outcomes in all population groups.

Progress Report/Summary of Accomplishments

Over the past year, the Project A research team has met both at full group level and also at small group level to discuss new research ideas, review progress of current analysis and identify next steps, and work on manuscript preparation.

We have spent considerable time linking the detailed birth record data to USEPA PM_{10}, $PM_{2.5}$, and ozone monitoring data in order to study the impact of *maternal exposure to air pollution* on birth weight. We are especially focused on refining exposure metrics to most effectively characterize meaningful exposures, as well as to capture any windows of vulnerability. Significant progress has been made on the relationship between birth outcomes and exposure to particulate matter and ozone separately, and the current focus is determining how to characterize joint exposure to both particulate matter and ozone. A manuscript on this work

appeared in the *Journal of Exposure Science and Environmental Epidemiology* (Gray et al., 2010). A critical issue in this work is addressing the misalignment between where monitoring stations are and where pregnant women live. Two approaches have been explored. One considers buffers of varying radii around monitoring sites to see how the exposure signal is affected by increasing distance from the site. The other attaches more uncertainty to the putative exposure as the distance from the monitoring site to the residence increases. Again, various exposure windows and metrics are considered. This work is forthcoming in *Statistics and Medicine* (Gray et al, 2011)

Related work has studied the use of a $PM_{2.5}$ exposure simulator to explain birthweight. In a recently submitted paper, a template is developed for using an *environmental dose simulator* to connect ambient exposure to personal exposure. Then, using various exposure metrics, calculated from these personal exposures, which are clinically plausible over the course of a pregnancy, linkage is built to adverse birth outcomes. This work has appeared in *Environmetrics* (Berrocal et al., 2011).

A substantial amount of effort this year has been devoted to a novel project concerned with connecting the *built environment* to adverse pregnancy outcomes. Built environment data has been collected under the Community Assessment Project and, after preliminary analysis has focused on spatial layers capturing four primary attributes of the built environment: housing damage, property disorder, tenure, and vacancy. Connection has been made to pre-term birth and low birth weight. Ongoing work is examining a bi-probit regression model as well as marginal logistic regressions. Future work will move from binary to continuous responses.

Our project on *racial residential segregation* has now seen the completion of one paper which enables quantification of racial exposure/isolation at finer spatial scales within SMSA's. Such a measure can be connected to measures of social and economic disadvantage at these scales to gain insight into how racial residential segregation has manifested itself across urban landscapes. In turn, this promises to reveal key insights into how to think about the spatial aspects of the social factors influencing health disparities. We are working to determine which facets of segregation best characterize the way community-level racial residential segregation acts to promote health disparities in birth outcomes. Although our initial efforts were statewide, we eventually decided that, given the significantly more detailed data available for Durham County, we would focus on this area to determine what variables are most important to characterizing racial residential segregation in terms of its health consequences. A paper was completed and now is forthcoming in the journal *Spatial and Spatio-temporal Epidemiology* (Anthopolos et al., 2011)

Another component of our work has focused on building *spatial downscalers*. Such modeling strategies enable the fusion of monitoring station data with computer model output to better assess environmental exposure at point level spatial resolution. Such downscalers can be dynamic, enabling the tracking of exposure through time. With improved estimation of local exposure, we can better examine linkage between exposure and adverse birth outcomes. Three papers on this methodology have been completed. The first, for the univariate case, appeared in the Journal of Agricultural, Biological and Environmental Statistics (Berrocal et al,

2010). The second considers the bivariate problem, looking at downscaling two exposures (ozone and PM2.5), borrowing strength in the joint modeling. This work has appeared in the *Annals of Applied Statistics* (Berrocal et al. 2010). Most recent work has focused on measurement error associated with downscaling. Such error is attributable both to misalignment between monitoring sites and model grids as well as to effects of neighboring grids on local monitoring site levels. This work is forthcoming in *Biometrics* (Berrocal et al., 2011).

Another recently completed manuscript builds *joint models for birthweight and gestational age* using bivariate normal mixtures. Such joint modeling adjusts for maternal risk factors and provides mixture analysis of the residuals to help illuminate further subpopulations with differential risk for adverse joint birth outcomes. Modeling of the mixture components is done through gestational age and then birthweight given gestational age. Joint modeling eliminates potential causal inference concerns. A paper has appeared in *Statistics in Medicine* (Schwartz et al., 2011). Follow-on work extends this work to incorporate spatial structure, introducing spatial random effects in the regression modeling for both outcomes.

We have also examined quantile regression methodology in explaining the effect of exposure on pregnancy outcomes. Here, the idea is that, rather than explaining mean birthweight as in customary regression models, we would be interested in explaining quantiles for birthweight. For instance, it would be of interest to explain the 10^{th} percentile of birthweight since this is the threshold for declaring low birthweight. It emerges that risk factors and environmental exposure affects different quantiles differently. (See Lum and Gelfand, in submission.)

In addition, we have completed work on specific analysis and manuscripts examining the impact of maternal age and birth order on birth weight (*Journal of Epidemiology and Community Health*, Swamy et al., 2011), on modeling ordinal categorical data using Gaussian processes (*Stochastic Modeling*, Heaton et al, 2011) and the etiology of racial disparities in maternal hypertensive disorders (*Public Health Report*s, Miranda et al., 2010).

We have completed considerable methodological work on expected performance accruing to *synthesizing categorical datasets* with the objective of enhancing inference. We are particularly interested in how to deal with a collection of datasets of varying sizes that are all relevant to a particular scientific question, but which include different subsets of the relevant variables, with some overlap. This work attempts to synthesize cross classified categorical datasets drawn from a common population where many of the sets are incomplete (i.e., one or more of the classification variables is unobserved), but at least one is completely observed. This is expected to reduce uncertainty about the cell probabilities in the associated multi-way contingency table as well as for derived quantities such as relative risks and odds ratios. We have made substantial progress on the underlying modeling and have developed a simulation example as well. We have also addressed the issue of the complete dataset not being a random sample from the population, as would be typical in practice. A manuscript on this work is presently in submission. (See Berrocal et al.)

Collaborations with other SCEDDBO Components

We have worked closely with the Project C investigators to design analysis looking at the same pollutants at comparative levels of exposure from different methodological perspectives. Our discussions with the investigators of Project C help inform our methods for framing ozone and particulate matter exposures in our models, as well as help refine the planning and implementation of future animal models in Project C. In addition, we regularly trade insights with Project B regarding appropriate ways to model the joint impact of social and environmental stressors on pregnancy outcomes. In particular, as the dataset being collected under Project B reaches a size and completeness suitable for analysis, we plan to bring some of the methodological strategies developed under Project A to this dataset including synthesis with the Detailed Birth Record data, the mixture modeling for birthweight and gestational age, and the refined environmental exposure approaches.

Future Activities

We plan to continue working on each of the areas described in the progress report/summary of accomplishments section. Achieving a better understanding of exposure to air toxins, particularly particulate matter and ozone, is a central focus of our future efforts. Areas of investigation will include space time analysis of trends in births across North Carolina, an investigation of linked births (same mother) using suitable random effects models, and a more thorough investigation of the impact of introducing spatial random effects in regression modeling to explain birth outcomes.

We recently began the process of linking participants in Project B with their associated birth certificate record. We are excited to begin exploring the additional insights into the detailed birth record data that can be gleaned by linking these data with the rich dataset collected in Project B. This linkage will not only allow us to explore issues of data accuracy in the detailed birth record, but will also allow us to begin implementing the methods of synthesizing categorical data discussed above.

We continue to target various professional audiences for dissemination of our work. Recent presentations have been at conferences under the auspices of the Joint Statistical Meetings, the American Public Health Association, the Society of Epidemiological Research, the International Biometric Society, and the Society of Maternal and Fetal Medicine.

Publications

Anthopolos, R, James, SA, Gelfand, AE, and Miranda, ML**.** A Spatial Measure of Neighborhood-level Racial Isolation Applied to Low Birthweight, Preterm Birth, and Birthweight in North Carolina. Forthcoming. *Spatial and Spatio Temporal Epidemiology.*

Berrocal, VJ., Gelfand, AE., Holland, DM., Burke, J., Miranda, ML.. On the Use of a $PM_{2.5}$ Exposure Simulator to Explain Birthweight. 2011, *Environmetrics*. 22(4), 553-571.

Chang HH, Reich BJ, Miranda ML. Time-to-Event Analysis of Fine Particle Air Pollution and Preterm Birth: Results from North Carolina 20001-2005. Forthcoming. *American Journal of Epidemiology.*

Gray, S, Edwards, S and Miranda, ML**.** Assessing Exposure Metrics for PM and Birth Weight Models. 2010. *Journal of Exposure Science and Environmental Epidemiology:* 20(5): 469-477. PMCID: PMC2889210.

Gray, SC., Gelfand, AE., Miranda, ML**.** Hierarchical Spatial Modeling of Uncertainty in Air Pollution and Birth Weight Study. Forthcoming. *Statistics in Medicine*.

Miranda, ML, Anthopolos, R, and Edwards, SE. Seasonality of Poor Pregnancy Outcomes. Forthcoming. *North Carolina Medical Journal.*

Miranda, ML, Edwards, SE, and Myers, ER., Adverse Birth Outcomes among Nulliparas versus Multiparas. Forthcoming. *Public Health Reports*.

Miranda, ML, Swamy, G, Edwards, S. Maxson, PJ, Gelfand, A, and James. S. Disparities in Maternal Hypertension and Pregnancy Outcomes: Evidence from North Carolina, 1994-2003. 2010. *Public Health Reports,* July/August 125(4):579-587. PMCID: PMC2882609.

Schwartz, S, Gelfand, A, Miranda, ML**..**Joint Bayesian Analysis of Birthweight and Censored Gestational Age using Finite Mixture Models. 2010 *Statistics in Medicine,* 20; 29(16):1710-1723.

Swamy, G. Edwards, S. Gelfand, A, and Miranda, ML. Maternal Age, Birth Order, and Race: Differential Effects on Birthweight. 2010 *Journal of Epidemiology and Community Health*. Published Online First: 15 November 2010. doi:10.1136/jech.2009.088567.

Publications – In Preparation/Submission

Chang HH, Reich BJ, Miranda ML. Spatial Time-to-Event Analysis of Air Pollution and Preterm Birth. Submitted.

Miranda, ML, Messer, LC, Kroeger, GL. The Impact of the Residential Built Environment on Pregnancy Outcomes. In revision.

Messer, LC, Neelon, B, Kaufman, JS. The Built Environment and Adverse Birth Outcomes: An Analysis using Biprobit Modeling to Account for Correlated Outcomes. In preparation.

Presentations

Chang HH, Reich BJ, Miranda ML. Spatial Time-to-Event Analysis of Preterm Birth and Fine Particulate Matter. Summer Research Conference, Southern Regional Council on Statistics, June 2010, Virginia Beach VA.

Chang HH, Reich BJ, Miranda ML. Time-to-Event Analysis of Preterm Birth and Fine Particulate Matter. Joint Statistical Meeting, Vancouver, Canada. Aug 2010.

Gray, S, Gelfand, A, Miranda, ML. Spatial Moeding of Uncertainty in Air Pollution and Birth Weight. Invited talk. Southern Regional Council on Statistics, June 2010.

Gray, S, Gelfand, A, Miranda, ML. Heirarchical Spatial Modeling of Air Pollution Exposure and Measurement Error. Joint Statistical Meeting. August, 2010.

Messer, LC, Miranda, ML. The Relationship between Resident-Defined and Census-Approximated Neighborhoods for Public Health Research: Inferential Implications. Society for Epidemiologic Research, Montreal, Canada, June 2010.

Messer, LC. The Built Environment and Women's Reproductive Health Outcomes. The Integrated Toxicology and Environmental Health Program Symposium. Duke University. March 25, 2011.

Supplemental Keywords
Data fusion, meta analysis, disparities, spatial disaggregation, spatial interpolation, spatial modeling, racial residential segregation

Research Project B: Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in Birth Outcomes

Period covered by the report: 5/1/2010 – 4/30/2011
EPA Agreement Number: RD83329301-0
Investigators: Redford Williams (PI), Allison Ashley-Koch, Richard Auten, Pamela Maxson, Marie Lynn Miranda, Jerome Reiter, Geeta K. Swamy
Project Period: Year 4

Objectives of Research

The central objective of the Healthy Pregnancy, Healthy Baby Study is to determine how the interaction of environmental, social, and host factors contributes to disparities in birth outcomes between African-American and white women in the American South. There are four specific aims:

1. Conduct a cohort study of pregnant women in Durham, NC designed to correlate birth weight, gestation, and birth weight x gestation with environmental, social, and host factors;
2. Develop community-level measures of environmental and social factors by inventorying neighborhood quality and the built environment in partnership with local community groups;
3. Create a comprehensive data architecture, spatially resolved at the tax parcel level, of environmental, social, and host factors affecting pregnant women by linking data from the cohort study and neighborhood assessments with additional environmental and socioeconomic data; and
4. Determine whether and to what extent differential exposures explain health disparities in birth outcomes by applying innovative spatial and genetic statistical methods to:
    a. Identify environmental, social, and host factors that cluster to predict birth outcomes in the entire sample,
    b. Determine whether these clusters are more or less present in African-American versus white populations and quantify the proportion of health disparities explained by differences in cluster frequency, and

c. Identify environmental, social, and host factors that cluster to predict birth outcomes within the African-American and white sub-samples and compare these clusters across racial groups.

Progress Report/Summary of Accomplishments

As of 4/1/2011, 1889 women have been enrolled in the study. Women are recruited from Duke University Medical Center (DUMC) and Lincoln Community Health Center. Demographic data indicate that we are successfully recruiting women who are most at risk for adverse pregnancy outcomes, particularly low-income, low educational attainment, and non-Hispanic black women.

The following information is collected from participants in the Healthy Pregnancy, Healthy Baby Study:

- Psychosocial measures include: CES-D, perceived stress, self-efficacy, interpersonal support, paternal support, perceived racism, perceived community standing, pregnancy intention, John Henryism Active Coping Scale, NEO Five Factor Inventory of personality.
- Environmental exposure survey measures include: short survey on fish consumption, smoking pattern and exposure to second-hand smoke, and drinking water source.
- Maternal and neonatal medical record abstraction includes: detailed pre-pregnancy medical and social history, antepartum complications, birth outcomes, and neonatal complications.
- Blood samples for genetic and environmental analysis to assess candidate genes related to environmental contaminant (nicotine, cotinine, cadmium, lead, mercury, arsenic, and manganese) metabolism, inflammation, vascular dysfunction, and stress response.
- Cord blood and placental samples are currently being stored for future genetic analysis and evaluation of activity at the maternal-fetal interface.

We have been highly successful in collection of participant-level data as well as biological samples, with greater than 90% attainment of maternal blood sample for genetic and environmental analyses. Collection of cord blood and placental samples, which began in June 2007, has also been successful with approximately 944 delivery samples collected.

All maternal data is georeferenced (i.e., linked to the physical address of the mother) using Geographic Information System (GIS) software. The Healthy Pregnancy/Healthy Baby Study also includes an in-depth neighborhood assessment designed to capture both built environment and community-level social stressors and community resources. The cohort study and neighborhood assessment data are spatially linked to extensive environmental and demographic data at a highly resolved spatial scale.

Genetic Data and Analysis. To date, we have generated genotypes on approximately 1600 blood samples from pregnant women. We have genotyped 412 Single Nucleotide Polymorphisms (SNPs) in fifty-two genes. Candidate genes include those involving human environmental contaminant clearance (heavy metals and environmental tobacco smoke), infection and inflammation (cytokines, chemokines, and bacterial pathogen recognition), maternal stress response (serotonin), and other pathways that have been implicated as potential drivers of health disparities (vascular responsivity).

In addition to our candidate gene data, we have generated the Illumina African American Admixture Chip on 1016 NHB women. This admixture chip contains 1509 SNPs which were specifically selected due to the disparate frequencies in the Yoruban (African) and European (Caucasian) HapMap samples, the two primary ancestral populations of NHB women. For the purpose of addressing population stratification, we have used clustering algorithms on the Illumina data to identify sub-populations within our NHB women and found that indeed some

stratification does exist. Thus, we have been using the genome-wide percentage of European admixture as a continuous covariate in our candidate gene analyses.

We have also used these data to examine the influence of ancestry on birth outcomes. African American women have greater risk than Caucasian women for adverse birth outcomes, even when controlling for social and demographic differences. However, many African American women have excellent birth outcomes, and a possible contributor is the percentage of European admixture. Clinical and genetic data were available for 848 non-Hispanic Black (NHB) women for the purpose of this analysis. Clinical outcomes analyzed included infant birth weight, pre-term birth (gestation < 37 weeks), birth weight less than 5th percentile for gestational age (SGA5), birth weight less than 10th percentile for gestational age (SGA10) and preeclampsia. 1509 SNPs were genotyped using the Illumina African American admixture panel. Six mitochondrial DNA (mtDNA) SNPs were genotyped via Taqman assays in order to construct ancestral mtDNA haplogroup (L0, L1, L2, L3, N, or R) for each subject. Among our NHB women, the genome-wide average percentage of European admixture was 17.9%. None of the clinical outcomes were associated with this estimate of European admixture. The distribution of subjects in each mtDNA haplogroup was: L0 (3.7%), L1 (18.5%), L2 (28.0%), L3 (39.9%), N (0.7%), R (9.3%). European admixture did not significantly differ among the 4 African mtDNA haplogroups (L0=17.3%, L1=17.4%, L2=17.6%, L3=16.7%). However, European admixture was higher among the women with mtDNA haplogroup R (24.4%, $p<0.0001$) compared with the African haplogroups. Clinical outcomes were also tested for association with African haplogroups. Women in the L3 haplogroup were more likely to deliver low birth weight (<1500g) babies than women in the L2 haplogroup ($p=0.004$). Women in the L3 haplogroup were also more likely to deliver SGA10 than women in the L2 haplogroup ($p=0.016$). These data suggest that NHB women in the L3 haplogroup, which originated in east Africa, are at greater risk for adverse birth outcomes than NHB women with the L2 haplogroup, which originated in western and sub-Saharan Africa. Thus, some measures of ancestral origin in African American women are correlated with differential risk for adverse birth outcomes. Additional analyses will be needed to determine whether the mtDNA haplogroups are a surrogate for mitochondrial function as previous studies may suggest (Scott et al., 2009). These results were submitted for presentation this fall at the International Congress of Human Genetics.

In previous progress reports, we have described our results regarding the influence of genetic variation in the Vitamin D receptor (VDR) gene, as well as the G-protein coupled receptor kinase 5 (GRK5) on infant and maternal outcomes, respectively. We have also described in previous reports our findings involving gene * environment interactions (G*E) among the inflammatory pathway and N-acetyltransferase genes with exposure to cadmium and environmental tobacco smoke. Thus, here we will focus on our more recent analyses on the effects of G*E among inflammatory SNPs and exposure to air pollution on infant birthweight.

The inflammatory response influences risk for adverse birth outcomes such as low birthweight. Variability in maternal inflammatory response may be exacerbated by exposure to air pollution during pregnancy. We examined how variation in maternal inflammatory genes interacts with air pollution to affect infant birthweight (BWT) in 673 non-Hispanic black (NHB) women participating in the Healthy Pregnancy, Healthy Baby Study. Maternal residential address at enrollment was georeferenced and the distance to the nearest major roadway was calculated as a proxy for traffic-related air pollution exposure. 105 haplotype tagging SNPs were genotyped in 20 candidate genes on maternal DNA samples. Linear regression was used to examine the relationship between SNPs and infant BWT, adjusting for infant sex, maternal age, parity, education, insurance, and smoking use. We also examined interactions between SNPs and roadway proximity. Nominal evidence for main effects on infant BWT was detected with *CR1*

(rs17047661, p=0.006), *IL10* (rs1518111, p=0.008), 2 SNPs in *IL8* (rs2227538, p=0.01; rs2227306, p=0.02), *IL12B* (rs2853694, p=0.03), *IL6* (r s2069840, p=0.03) and *IL12A* (rs568408, p=0.04). Evidence for SNPs interacting with roadway proximity to influence BWT was detected with two SNPs in *TLR4* (rs12344353, p=0.01; rs5030725, p=0.03), two SNPs in *IL4* (rs2227282, p=0.008; rs2243283, p=0.03) and one SNP in *INFG* (rs2069714, p=0.04). Consistent with previous reports, genetic variation in the inflammatory response provided evidence for main effects on infant BWT among NHB women in our study. We provide the first evidence that some of these genes interact with air pollution exposure to influence infant BWT. These results are being written for publication and also have been submitted for presentation at the International Congress of Human Genetics, this fall.

Psychosocial Indicators. Analyses have been completed on psychosocial influences on birth outcomes. The relationships among pregnancy intention, psychosocial health, and pregnancy outcomes have been examined, with a paper accepted. In addition, we are examining pregnancy intention, behavioral choice, and environmental exposures. The influences of psychosocial health and smoking status have been studied, and a paper has been submitted. In order to reduce the number of psychosocial variables, cluster analysis has been performed, resulting in three distinct clusters of women. Cluster analysis on the personality indices were also performed. A resulting paper presented at the Society of Behavioral Medicine meeting reported that women with an adverse personality profile were more likely to express several psychosocial risk factors (e.g., increased depressive symptoms, increased unwanted pregnancy) and had a six-fold higher rate of preterm (<32 weeks) delivery than women with a resilient profile. We are currently preparing a manuscript reporting these findings for submission to a journal and also submitted an STTR grant to NICHD to adapt the Williams LifeSkills Workshop for use as an intervention to improve pregnancy outcomes in women at high risk. Although this grant proposal was not funded, we plan to resubmit in year 5.

Maternal Medical Complications. Fetal health is not only individually determined, but is also influenced by maternal health and well-being. This past year, we have begun to examine maternal outcomes, as well. In particular, we have begun to focus on hypertensive disorders during pregnancy. As a first step, we are trying to identify factors that affect maternal blood pressure during pregnancy. In order to make use of the entirety of blood pressure readings collected across the pregnancy, we are considering a variety of statistical approaches, including latent trajectory and sparse functional data models. Our goal is to use environmental, social and genetic data (such as GRK5 polymorphisms) to predict these blood pressure trajectories. Ultimately we hope these predicted trajectories will aid us in predicting birth outcomes; for example, women with monotone-increasing blood pressure trajectories may exhibit poorer birth outcomes than women with U-shaped curves. This work has been done in collaboration with the GISSA core.

Statistical Methods Development. We developed several new statistical methodologies designed to improve analysis of the Project B data, as well as to advance statistical analysis more broadly. First, we developed and implemented methods for finding important predictors in quantile regression when there are a very large number of covariates. These methods adapted the lasso and elastic net penalties for quantile regression. We applied the methods on a mid-study sample of women to uncover a previously unreported interaction: women who smoke and who have high blood lead levels tend to have babies with lower birth weights. An article on this research has been accepted for publication by *Epidemiology.*

Second, we developed and implemented methods for using factor analysis models in the

context of quantile regression. The investigative team believes that many of the predictors can be grouped into underlying factors. For example, the Project B data contain several variables that measure maternal stress, and arguably we should connect birth outcomes to the underlying factor of stress rather than its individual indicators. As another example, the data contain several imperfect indicators of smoking status, and we would like to connect birth outcomes to the underyling factor of true smoking status. We implemented the model on a mid-study sample of women from Project B, and we found that the smoking factor was a strong predictor of low birth weight. An article on this research was accepted for publication in *Biometrics.*

Third, we developed and implemented methods for accounting for mid-study changes in measurement scales. These methods were needed because the Project B investigators switched assay labs for measuring blood levels of heavy metals midway through data collection in order to take advantage of finer measurement scales. Exploratory analysis indicated that the distributions of levels for several exposures were markedly different across the labs, so that analyses based on a simple concatenation of the two labs' data would be biased. Using the second lab scale as the standard, so that effectively measurements before the lab switch are treated as missing, we developed general purpose methodology for imputing plausible values of the missing exposure measurements. The methods are based on assumptions about the relative ranks of measurements in the two scales, e.g., a measurement in the 10^{th} percentile in one scale should be at the 10^{th} percentile in the other scale. We implemented this methodology on the Project B data to provide the investigative team with improved data product. An article on the methodology for this research was accepted to the *Journal of the American Statistical Association.*

We also developed a Bayesian growth mixture model to jointly examine the associations between longitudinal blood pressure measurements, preterm birth (PTB), and low birthweight (LBW). The model partitions women into distinct classes characterized by a mean arterial pressure (MAP) curve and joint probabilities of PTB and LBW. Each class contains a unique mixed effects model for MAP with class-specific regression coefficients and random effect covariances. To account for the high correlation between PTB and LBW, we introduce a bivariate probit model within each class to capture residual within-class dependence between PTB and LBW. The model permits the association between PTB and LBW to vary by class, so that for some classes, PTB and LBW may be positively correlated, while for others, they may be uncorrelated or negatively correlated. We also allow maternal covariates to influence the class probabilities via a multinomial logit model. For posterior computation, we propose an efficient Markov chain Monte Carlo algorithm that combines full-conditional Gibbs and Metropolis steps. We apply our model to a sample of 1027 women enrolled in the Healthy Pregnancy, Healthy Baby Study, a prospective cohort study of host, social, and environmental contributors to disparities in pregnancy outcomes. A manuscript based on this work has been accepted for publication at *Statistics in Medicine*.

We also focused statistical methods development on the genetic data. The first statistical innovation involving the genetic data is the adverse sub-population regression (ASPR) for multi-variate outcomes with high dimensional predictors. The ASPR is a two component latent class model, with the dominant component corresponding to (presumed) healthy individuals and the risk of falling in the minority component characterized via a logistic regression. The logistic regression model is designed to accommodate high-dimensional predictors, as occur in studies with a large number of gene by environment interactions, through use of a flexible nonparametric multiple shrinkage approach. The Gibbs sampler is developed for posterior computation. The method was evaluated with the Project B data and has been submitted for publication.

The second innovation involving the genetic data was motivated by our analysis of the admixture data. The current genetic analysis tool that is most widely used (ANCESTRYMAP) is very limited in that it only allows consideration of qualitative, not quantitative, outcomes and does not allow for the incorporation of covariates. Thus, we have extended this method and it will be submitted for publication this summer. It has also been submitted for presentation at the International Congress of Human Genetics this fall.

Collaborations with other SCEDDBO Components

The collaborative efforts across the SCEDDBO components have continued to increase over the past year. The entire SCEDDBO team prioritized air pollution as one of the primary environmental contaminants to be examined across projects. This has involved significant discussions between members of Project B with members in Project A to construct viable markers of air pollution, including proximity to major roadways, and NATA data. Project B also prioritized the interleukin/inflammatory genes for analysis after consultation with Project C so that we could make more biological synergies across the two projects. Similarly, Project C introduced a nest-deprivation model into the ongoing animal experiments in an attempt to better replicate the more complex psycho-social stressors experienced by the mothers in Project B. And finally, the statistical team for the GISSA has worked hard to develop more innovative statistical approaches to disentangling the complex web of interactions that are driving the birth outcomes. These innovations have been motivated by specific questions across all three projects.

Future Activities

In the next year, we will focus on data analysis and further statistical methods innovation. Our primary interest is in bringing these two pieces together. The statistical methods innovation is driven by the needs of our data analysis and thus will continue to explore means to reduce the dimensionality of the genetic and other data, as well as impute missing data. Our overall goal is to identify complex interactions amongst the three sides of the triangle we hypothesize influence pregnancy outcomes: host, social, and environmental contributors. As a direct result of this focus on data analysis, we anticipate preparing and publishing several manuscripts in year five. With the bulk of our data collection now complete, we will are well-positioned to examine and identify combinations of factors that lead to health disparities in birth outcomes. We are particularly interested in identifying environmental risk factors given that they are actionable to improve birth outcomes.

Publications

Burgette, LF, Reiter, JP. Multiple Imputation via Sequential Regression Trees. 2010. *American Journal of Epidemiology*, *172*, 1070-1076.

Burgette, LF, Reiter, JP, and Miranda, ML. Exploratory Data Analysis for Quantile Regression: An Application to Adverse Birth Outcomes. Forthcoming. *Epidemiology.*

Burgette, LF, Reiter, JP. Modeling Adverse Birth Outcomes via Confirmatory Factor Quantile Regression. Forthcoming. *Biometrics*.

Burgette, LF, Reiter, JP. Nonparametric Bayesian Multiple Imputation for Missing Data due to Mid-Study Switching of Measurement Methods. In revision.

Maxson PJ, Miranda ML "Pregnancy Intention, Demographic Differences, and Psychosocial Health." Forthcoming. *Journal of Women's Health.*

Miranda ML, Edwards S, Maxson PJ. Mercury Levels in an Urban Pregnant Population in Durham County, North Carolina. 2011. *International Journal of Environmental Research in Public Health,* Mar 8(3):698-712.

Miranda, ML Edwards, SE Swamy, G Paul, C and Neelon.B. Blood Lead Levels among Pregnant Women: Historical versus Contemporaneous Exposures. 2010. *International Journal of Environmental Research and Public Health* 7(4): 1508-1519.

Neelon B, Swamy GS, Burgette LF, and Miranda, ML. A Bayesian Growth Mixture Model to Examine Maternal Hypertension and Birth Outcomes. 2011*. Statistics in Medicine.*

Schwartz, S, Li, F, and Reiter, JP. Sensitivity Analysis for Unmeasured Confounding in Principal Stratification. In revision.

Swamy, GK, Garrett, ME, Miranda, ML, Ashley-Koch, AE. Maternal Vitamin D Receptor Genetic Variation Contributes to Infant Birthweight among Black Mothers. 2011. *American Journal of Medical Genetics Part A, 155,* 1264-71.

Publications – In Preparation/Submission

Ashley-Koch AE, Garrett ME, Edwards S, Swamy GK, and Miranda ML. Maternal Genetic Variation in Genes Involved in the Inflammatory Response Interact with Measures of Air Pollution Exposure to Affect Infant Birthweight among Non-Hispanic Black Women. In preparation.

Ashley-Koch, AE, Garrett, ME, Swamy, GK, Miranda, ML. Genetic Variation in NAT1 Interacts with Cadmium Exposure to Influence Pregnancy Outcomes in non-Hispanic Black (NHB) Women. In preparation.

Maxson, P, Edwards, S, Ingram, A, Miranda, ML. Psychosocial Differences Between Smokers and Non-smokers Suring Pregnancy. In submission.

Maxson, PJ, Messer, LC, Miranda, ML. Pregnancy Intention and Associations with the Built Environment. In preparation.

Messer, LC, Miranda, ML, Maxson, PJ. The Built Environment and Women's Psychosocial Health. In preparation.

Swamy, GK, Garrett, ME, Miranda, ML, Ashley-Koch, AE. Genetic Variation in G-Protein Coupled Kinase Receptor 5 and Preeclampsia. In preparation.

Zhu B, Dunson D, Ashley-Koch AE. Adverse Sub-population Regression for Multivariate Outcomes with High-dimensional Predictors. In submission.

Presentations

Ashley-Koch AE, Swamy GK, Garrett ME, Quinn KS, Buskwofie A, Miranda ML. Genetic Variation in NAT1 Interacts with Cadmium Exposure to Influence Pregnancy Outcomes in Non-Hispanic Black Women. American Society for Human Genetics, Washington, DC, 2010.

Burgette, LF, Reiter, JR. Modeling Adverse Birth Outcomes via a Factor Model for Bayesian Quantile Regression. Joint Statistical Meeting. August, 2010.

Buskwofie A, Swamy GK, Garrett ME, Quinn KS, Buskwofie A, Miranda ML, Ashley-Koch, AE. Genetic variation in the inflammatory pathway contributes to preeclampsia in non-Hispanic black women. American Society for Human Genetics, Washington, DC, 2010.

Maxson, PJ, Miranda, ML. Prenatal depression risk and resilience. Society of Prenatal Epidemiological Research. Seattle, WA, June 2010.

Maxson PJ, Miranda ML, Williams RB. Personality and Health during Pregnancy. Society of Behavioral Medicine, Washington, DC, April 2011.

Maxson, PJ, Edwards, SE, Miranda, ML. Maternal Psychosocial Health and Prenatal Exposure to Tobacco. Pediatric Academic Society, Denver, CO, April 2011

Maxson, PJ, Miranda, ML. Psychosocial Health and Risk during Pregnancy. Society of Maternal and Fetal Medicine, San Francisco, CA, February 2011.

Maxson, PJ, Reiter, J, Miranda, ML. Psychosocial Health and Risk during Pregnancy: A Cluster Analytic Approach. Society of Epidemiological Research. Seattle, WA, June 2010.

Miranda, ML, Maxson, PJ. Environmental Exposures, Pregnancy Intention, and Behavioral Choice. Pediatric Academic Society. Vancouver, Canada, May, 2010.

Swamy, G, Miranda, ML, Neelon, B. Association between maternal blood pressure trajectories and adverse birth outcomes. Aspen Perinatal Biology Conference. Aspen, CO, August, 2010.

Supplemental Keywords
Pregnancy, preterm birth, low birth weight, racial disparity, African American, environmental stressors, gene-environment interactions, psychosocial stressors, genes, single nucleotide polymorphisms, genetic admixture

Research Project C: Perinatal Environmental Exposure Disparity and Neonatal Respiratory Health

Period covered by the report: 5/1/2010 – 4/30/2011
EPA Agreement Number: RD83329301-0
Investigators: Richard L. Auten (P.I.), W. Michael Foster
Project Period: Year 4

Objectives of Research:

The specific aims of Research Project C, titled Perinatal Environmental Exposure Disparity and Neonatal Respiratory Health, are:

1. To determine whether maternal exposure to airborne particulates (PM) and/or ozone (1st hit) restricts fetal growth and/or postnatal growth, and impairs lung development/function in newborn mice;
2. To determine whether PM and/or ozone exposure 're-programs' maternal inflammatory responses;
3. To determine whether postnatal (2nd hit) ozone exposure further impairs postnatal somatic and lung development/function following maternal PM and/or ozone exposures;
4. To determine whether genetic or developmental susceptibility to airway hyperreactivity exacerbates maternal and/or postnatal exposure effects on postnatal somatic and lung development/function.

Progress Report/Summary of Accomplishments

1. Aim 4 was focused on genetic susceptibility. To determine which pathways are important to transducing maternal air pollutant exposures to adverse effects on fetuses and newborns, we have conducted studies in mice lacking the Tlr4 gene, a key innate immune response receptor previously shown to be important to acute ozone induced airway hyperreactivity in adult mice. Our studies have shown that the placental, fetal lung, and fetal brain cytokines that were induced by maternal diesel inhalation are in many cases dependent on maternal+fetal Tlr4 signaling. In particular we have found that the maternal diesel inhalation/instillation effects on IL-1β, IL-6, KC, TNFα, and eotaxin responses in the placenta, and IL- β, TNFα, and MIP-1, and RANTES in the lung are dependent on Tlr4.
2. Increasing evidence points to epigenetically mediated heritable effects of environmental pollutant exposures on health outcomes. We have conducted studies using the diesel particle described in the prior Progress Report to test this concept. Maternal diesel exposure increases the vulnerability of offspring to inflammatory airway challenge with nebulized endotoxin, a ligand for Tlr4. Studies done in collaboration with J. Hollingsworth and D. Brass suggest these increased susceptibilities are epigenetically mediated, with inheritance of the diesel exposure effect to the F3 generation. Current studies are aimed at identifying specific molecular pathways that may be responsible.
3. Since the last reporting period, we have conducted additional studies on the effects of resource deprivation (nest/housing restriction) in combination with maternal pollutant (diesel) exposure and found that the combination impairs postnatal weight gain and worsens the response to inflammatory endotoxin challenge. We did not observe effects on airway hyperresponsiveness, but do not expect this without the contribution of post-natal ozone exposure. These studies suggest that the combination of sub-clinical chemical and non-chemical stressor exposures have important effects on lung susceptibility to inflammatory challenge in offspring at a juvenile stage of development. The extension of our studies to include these components is funded by a Duke Integrative Brain Sciences incubator award that was competitively renewed for FY11-12.
4. We are finishing our studies on the neural contributions towards ozone induced airway hyperresponsiveness and a manuscript is in preparation.
5. Since oxidative stress is an important pathway implicated in ozone induced asthma in children, we sought to determine whether an asthma susceptibility gene, NQO1 (NAD(P)H quinone oxidoreductase-1) was also important in conferring airway

hyperresponsiveness in our animal model. We have completed studies showing that *Nqo1* null mice are completely protected from the effects of neonatal ozone exposure on prolonged airway hyperreactivity that persists to adulthood. This strongly implicates the oxidative stress responses during early life in the development of later airway hyperreactivity. We are repeating some of the pivotal experiments to confirm this. In contrast with our studies of combined maternal diesel and postnatal ozone exposure, we did not find substantial effects of ozone, with or without *Nqo1* knockout, on alveolar development.

Collaborations with other SCEDDBO Components

1. The elements from the prior reporting period are unchanged.

Future Activities

1. We are continuing to determine the contribution of combined chemical and non-chemical perinatal stressors on respiratory and neurocognitive development of offspring. We are extending our studies using the Tlr4 null mice to determine the contribution of either maternal innate immune responses or fetal/neonatal immune responses to the adverse effects of the combined stressors on lung and brain development.
2. The epigenetic contributions will be studied in more detail by evaluating particular molecular pathways in pulmonary macrophages which appear to be critical to the effects on airway hyperreactivity in mice born to dams exposed to diesel inhalation.

Publications

1. Auten RL and Foster WM. Biochemical Effects of Ozone on Asthma Development. *BiochimicaetBiophysicaActa*, in press.
2. Auten RL, Gilmour MI, Potts EN, Mason SN, Foster WM. Maternal diesel inhalation increases airway hyperreactivity in ozone exposed offspring. Submitted.
3. Auten RL, Mason SN, Potts EN, Chitano P, Foster WM. Neonatal murine ozone exposure induces neutrally mediated airway hyperreactivity persisting to adulthood. In preparation.

Presentations

1. U.S. EPA October 18, 2010. “Combining Air Pollution Exposures with Resource Deprivation: Lessons from Mouse Models” *Protecting Children’s Health for a Lifetime: Environmental Health Research Meets Clinical Practice*
2. Auten, R. Neonatal ozone-exposure induced airway hyperresponsiveness is mediated by afferent innervations. Pediatric Academic Society, Vancouver, Canada, May, 2010.

Supplemental Keywords

Epigenetic, innate immunity, Nqo1

Annual Reporting Form for SCEDDBO Projects and Cores

Title of Project/Core: Community Outreach and Translation Core

Period covered by the report: 5/1/2010 – 4/30/2011
EPA Agreement Number: RD83329301-0
Investigators: Martha H. Keating/Pamela Maxson
Project Period: Year 4

Objectives of Research

The central objective of the Community Outreach and Translation Core (COTC) is to create, implement, and assess strategies to translate and apply the findings of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO) into relevant information for women of childbearing age, families, community groups, policy makers, and health care professionals. The COTC conducts environmental health outreach and education directed at low income and minority women and their children; enhances the capacity of disadvantaged communities to understand threats posed by environmental contaminants; and provides a bridge between campus research, communities and policy makers. The specific aims of the COTC are:

1. Support the community-based neighborhood assessment being undertaken as part of Research Projects A and B;
2. Partner with nursing programs at Duke-affiliated hospitals to develop and present curricula to nursing students on environmental exposures and maternal and child health outcomes;
3. Develop culturally-appropriate advisory materials on environmental contaminants for low-income expectant or nursing mothers with low English proficiency;
4. Deliver training to local health department personnel focused on environmental factors related to maternal health and pregnancy outcomes;
5. Participate in regional, state and federal policy dialogues to provide decision makers with policy-relevant science-based information concerning environmental exposures and health disparities related to maternal and child health and well-being; and
6. Increase awareness of maternal health and health disparities by facilitating bi-directional exchanges between Center investigators, community members, public health advocacy groups, and policy makers.

Progress Report/Summary of Accomplishments

The goals for COTC in Year 4 were to continue to expand communication and translation efforts to specific audiences. With a communication strategy in place, the COTC utilized various communication tools appropriate to a variety of audiences. Collaboration with researchers and groups external to SCEDDBO continued to evolve and the COTC welcomed and responded to requests for environmental health information from community groups and the general public.

In Year 4, the COTC continued to disseminate the findings of the Community Assessment Project (CAP) which assesses built environment variables for over 17,000 tax parcels, including the home addresses of over 40% of the participants in the Healthy Pregnancy, Healthy Baby

Study (SCEDDBO Project B). During Year 4, the CAP methodology and findings were presented at a SCEDDBO-sponsored symposium on the Social Context of Environmental Exposures in Children and the Region 4 PEHSU Break the Cycle conference.

Although data collection for CAP has concluded, the project is not static. CAP data are being summarized through the development of Neighborhood Health Indices which describe seven major characteristics of neighborhoods that potentially affect health (e.g., tenure, safety, housing and property damage). Development of the indices has facilitated linking the CAP findings to Projects A and B pregnancy outcomes. Several manuscripts based on this work will be submitted during Year 5.

Specific Aim 2 of the COTC is to partner with nursing programs to develop and present curricula to nursing students on environmental exposures and maternal and child health outcomes. Implementing activities to address this Specific Aim continued as a focus of COTC efforts in Year 4. A comprehensive project was designed to develop environmental health curricula for nursing students, nursing faculty, and practicing nurses. Supplemental funding was sought with a grant submittal to EPA's Environmental Education Grant Program. The COTC was awarded the supplemental funding and collaborations have been ongoing with the Duke School of Nursing and the UNC School of Nursing. Work on this project will continue in Year 5. COTC staff continues to collaborate with a variety of regional, state, and federal advisory groups including the American Lung Association Advisory Group, the Durham County Health Department Community Health Assessment Working Group, and the Obesity and Chronic Disease Committee of the Partnership for a Healthy Durham. In addition, SCEDDBO Director Marie Lynn Miranda serves on the EPA's Children's Health Protections Advisory Committee (CHPAC). The CHPAC is a federal advisory committee established in 1998 to provide independent advice to the EPA Administrator on regulations, research, and communications issues relevant to children's environmental health.

Collaborations with other SCEDDBO Components

COTC staff continues to meet monthly with the SCEDDBO investigators to keep apprised of research developments and findings, translation opportunities, and scientific outreach activities (e.g., meetings, presentations and manuscripts) of the SCEDDBO investigators. The COTC staff also provides the investigators with updates on COTC activities and opportunities to participate in outreach activities. During Year 4, as part of the communication strategy, COTC staff received a periodic update from each SCEDDBO investigator detailing any presentations, conferences, or other issues or occasions that might constitute a research translation opportunity. These regular and frequent communications enable COTC staff to keep abreast of research progress, update the website, and plan for translation efforts.

External Collaborations

The COTC has developed a wide and diverse network of collaborators among federal, state and local agencies, universities and community groups. Activities with these diverse partners cover a broad spectrum of children's environmental health issues, ranging from birth outcomes to lead poisoning prevention, environmental exposures, and obesity.

COTC has developed relationships with the Duke Watts School of Nursing and the University of North Carolina School of Nursing to provide environmental health education to nursing students. To this end, COTC co-sponsored a one-day symposium for nurses in May, 2010,

"Environmental Considerations in Nursing Practice." In addition, SCEDDBO provided training to nursing students on Geospatial Information Systems in a one-day workshop.

COTC staff has developed working relationships with scientists at the U.S. EPA representing a wide variety of disciplines. These relationships have allowed for exchange of research findings and data in a number of areas including distance-to-roadway analyses, air pollution impacts on birth outcomes, community engagement, and using GIS for environmental justice analysis. In terms of formal meetings, Activities with multiple state and local agencies continue to cover a wide variety of topics including the impact of the built environment on obesity and pregnancy outcomes, mapping environmental exposures and built environment variables, as well as other topics related to school-aged children. The COTC is actively working with staff at numerous state and local offices. At the state government level these offices include the Senior Advisor for Healthy Schools, the Women's Health Branch, the Nutrition Services Branch, and the Office of Healthy Carolinians. Activities with county health departments and non-profit organizations ranged from GIS training and fulfilling mapping requests to serving on advisory groups (for example Durham County's Community Health Assessment Working Group).

For the 3rd consecutive year, COTC investigators mentored a student in the "Break the Cycle" project sponsored by the Region 4 of the U.S. EPA, Emory University and the Southeast Pediatric Environmental Health Specialty Unit. The selected student presented the built environment data from our Community Assessment Project and its relationship with pregnancy outcomes. The conference was held in Atlanta, GA, in May 2010. Dr. Pamela Maxson accompanied her as her mentor.

Finally, the COTC continues to respond with detailed information to numerous requests from private citizens about a variety of environmental health concerns. These requests were received through both the CEHI toll-free number and via the CEHI website.

Future Activities

During year 5, the COTC will continue to expand communication and translation efforts to specific audiences. By participating in the design, planning, and execution of the Durham County Community Health Assessment, we hope to gain additional insight into community health and information needs. The second wave of the Community Assessment Project will occur during Year 5, which will enable us to expand our capture rate of the participants in the Healthy Pregnancy, Healthy Baby study as well as validate our earlier findings. We will also continue our efforts to incorporate environmental health topics into continuing nursing education and sustain established collaborations with researchers within and external to SCEDDBO.

Publications

Presentations

Miranda, ML. Environment Matters: An Overview of Public Health and the Environment. Environmental Health Nursing Conference. Chapel Hill, NC. May 2010.

Ouyang, R., Keating, M., Maxson, PJ. There Goes the Neighborhood: The Relationship between the Built Environment and Birth Weight in Central Durham, NC. Break the Cycle, Atlanta, GA, May 2010.

Supplemental Keywords

Risk communication, outreach, translation, participatory research, built environment

Geographic Information System and Statistical Analysis Core

Period covered by the report: 5/1/2010 – 4/30/2011
EPA Agreement Number: RD83329301-0
Investigators: Alan Gelfand (PI), Allison Ashley-Koch, Marie Lynn Miranda, Jerome Reiter
Project Period: Year 4

Objectives of Research

The overall objective of the GIS and Statistical Analysis Core is to support spatial and quantitative analysis needs of the Center research projects, as well as the Community Outreach and Translation Core. Our specific aims include:

1. Providing support for the development of environmental and social data layers needed to implement data analyses required for the research projects and the Community Outreach and Translation Core;

2. Providing statistical analysis, advice, and consulting on the broad range of statistical issues that arise in conjunction with the research projects, with a particular emphasis on data reduction methods and modeling spatial and spatio-temporal data within a Bayesian framework; and,

3. Providing analysis for the unique needs of genetic data arising from the clinical and animal studies of the center.

This support core facilitates the development of innovative quantitative methodology for children's environmental health research associated with the projects and cores. Equally important, it will enhance substantive collaboration between statisticians and scientists involved in the research projects yielding improved analyses of research core data, as well as novel statistical modeling.

Progress Report/Summary of Accomplishments

In the fourth year of the project, the GISSA Core has continued to focus on developing the data warehouse providing underlying support for all other Center components. We have acquired and georeferenced additional detailed birth record data, continued genotyping blood samples from the participants in Project B, and continued providing data management support as Project B continues to enroll additional participants and conduct quality control/quality assurance on participants who completed the study in previous years.

This year we received and processed the 2009 individually-identified North Carolina Detailed Birth Records (DBR), giving us access to 19 years of birth data covering 1990-2009. The DBR is compiled from questionnaires obtained at the time of birth certificate filing and includes elements essential to our proposed analyses. Available variables include, *inter alia*: maternal

residence and state and country of birth; marital status; maternal and paternal race, Hispanic ethnicity, and education; alcohol and tobacco use; plurality; parity; maternal complications; congenital anomalies; whether an infant death certificate was filed; and infant birth weight and gestational age. All 19 years of data have been integrated and standardized to facilitate data linkages and statistical analysis.

We have expanded the environmental data layers available for use through the SCEDDBO data warehouse. These include spatial data on road intensity, criteria air pollutants from the USEPA's AQS system, water quality, environmental releases documented in the Toxics Release Inventory, and housing quality.

We have developed methods for linking the North Carolina DBR data with other clinical and administrative and clinical datasets. These methods rely on the individually-identifying variables provided in the DBR, including full name and date of birth of both infant and mother. We first applied this methodology to link DBR data with participant data from Project B, matching participants who delivered between 2005 and 2009 to their corresponding record in the DBR. This linkage will allow us to examine how accurately the administrative dataset (DBR) captures key information, as well as undertake analysis of residential mobility during pregnancy. Using the 1990-2007 DBR, we have linked births occurring to the same mother. This linkage allows us to examine internatal spacing and birth outcomes across pregnancies, and by further combining this data with the DBR-linked Project B data, we will be able to capture the participants' subsequent pregnancy outcomes. In addition, we have used this method to link the DBR data with an administrative datasets of educational outcomes at the individual child level, which will allow us to examine how disparities in birth outcomes may have long-term implications for child development.

To date, we have genotyped 1600 blood samples from pregnant women for 412 Single Nucleotide Polymorphisms (SNPs) in fifty-two genes, primarily involved in either metabolism of heavy metals or immune response. In addition, we have generated the Illumina African American Admixture Chip on 1016 NHB women. With these data now available, we have begun statistical analysis looking at environmental and genetic contributions and interactions to pregnancy outcomes. These results are discussed in the Project B report. We anticipate further genotyping and statistical analysis in the coming year.

Collaborations with other SCEDDBO Components

By its nature, the GISSA Core is highly involved in collaborations across all Center components. We are working with the investigators of Project A to determine what spatial data layers need to be developed and at what spatial scales. We are also expanding and supporting the data architecture to facilitate linkages of the data compiled by Projects B and C in order to create opportunities for synergies across projects.

Future Activities

We will continue developing and expanding the geospatial data warehouse that supports analysis among various projects. The GIS team will continue working with investigators in Projects A and B to develop a comprehensive list of environmental spatial data layers of interest, as well as a plan for prioritizing the development of this crucial dataset.

We will continue analyses on approximately 1,600 Project B participants with complete pregnancy data, genetic results, and environmental results. Analyses will look at the joint impact of environmental, social, and host factors on birth outcomes, especially as they differ by and within race. Identification of such co-exposures could lead to development and

implementation of strategies to prevent adverse birth outcomes, ultimately decreasing or eliminating the racial disparity. We will also continue to generate imputed datasets based on the methodology developed by the GISSA Core, in order to handle missing data.

As Project B continues to enroll participants, maternal blood samples will be analyzed for genetic and gene x environment associations with adverse birth outcomes. Additional genotyping will involve genes in the maternal stress response and vascular/endothelial cell dysfunction pathways. Statistical analysis regarding candidate gene polymorphisms has already begun and will continue in Year 5.

Publications
All manuscripts supported by the GISSA Core are listed under the individual research projects.

Supplemental Keywords
Data fusion, meta analysis, disparities, spatial disaggregation, spatial interpolation, spatial modeling